IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re Application of: James P. Elia	)	
	)	Group Art Unit: 1646
Serial No.: 09/064,000	)	
	)	Examiner: Elizabeth C. Kemmerer, Ph.D.
Filed: April 21, 1998	)	
	)	
For: METHOD FOR GROWTH OF SOFT TISSUE	)	

SECOND SUPPLEMENTAL DECLARATION
OF ANDREW E. LORINCZ, M.D.

I Andrew E. Lorincz declare as follows:

1. I reside at 16135 NW 243rd Way, High Springs, Florida 32643-3813.

2. My Curriculum Vitae is attached as Exhibit A to my Declaration of February 12, 2001. Paragraph 4 of my Declaration and my Supplemental Declaration of November 8, 2004 provide additional information regarding my background and experience.

3. I have read and understood the disclosures of the above-referenced patent application at page 20, line 10 through page 21, line 15; at page 37, lines 19-25; at page 44, line 19 through page 46, line 16; and at page 47, line 22 through page 48, line 15. Such disclosures are the same as I read and understood in my

previous Declaration. A copy of such disclosures is attached hereto as Second Supplemental Declaration Exhibit A.

I have also read and understood additional disclosures of the above-referenced patent application at page 33, lines 8-10; page 40, line 20 through page 43 line 3; page 44, lines 12 and 13; page 48, lines 13-15; page 53, line 1 through page 56, line 25; and page 62, lines 1-10. A copy of such additional disclosures is attached hereto as Second Supplemental Declaration Exhibit B.

4. I note that the disclosures referenced in above Paragraph 3 relate to using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, such as a stem cell, to grow soft tissue, such as an artery.

5. I have read and understood the claims set forth in the attached Second Supplemental Declaration Exhibit C and have been informed that such claims will be concurrently presented in the above-referenced patent application with this Second Supplemental Declaration.

6. Based upon above Paragraphs 3-5, it is my opinion that introducing a growth factor, including cells, and more specifically, stem cells, in the body of a human patient will predictably result in the growth of soft tissue, such as an artery, which will integrate itself into pre-existing tissue of the body thereby forming a unified whole.

7. Based upon above Paragraphs 3-5, it is my opinion that one skilled in the medical arts, armed with the knowledge in such paragraphs, would be able to practice the method set forth in Exhibit C without need for resorting to undue experimentation.

8. Declarant states that the above opinion was reached independently.

Declarant understands that (1) any willful false statements and the like made herein are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon, and (2) that all statements made of Declarant's own knowledge are true and that all statements made on information and belief are believed to be true.

Further Declarant sayeth not.

Date: 5 June 2006

Andrew E. Lorincz, M.D.

Andrew E. Lorincz, M.D.

EXHIBIT A

DISCLOSURES
APPLICATION SERIAL NO. 09/064,000

PAGE 20, LINE 10 – PAGE 21, LINE 15

Growth factors can be utilized to induce the growth of "hard tissue" or bone and "soft tissues" like ectodermal and mesodermal tissues. As used herein, the term growth factor encompasses compositions and living organisms which promote the growth of hard tissue, such as bone, or soft tissue, in the body of a patient. The compositions include organic and inorganic matter. The compositions can be genetically produced or manipulated. The living organisms can be bacteria, viruses, or any other living organism which promote tissue growth. By way of example and not limitation, growth factors can include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (acidic/basis (FGF a,b), interleukins (IL's), tumor necrosis factor (TNF), transforming growth factor (TGF-B), colony-stimulating factor (CSF), osteopontin (Eta-1 OPN), platelet-derived growth factor (PDGF), interferon (INF), bone morphogenic protein 1 (BMP-1), and insulin growth factor (IGF). Recombinant and non-recombinant growth factors can be utilized as desired. Bacteria or viruses can, when appropriate, be utilized as growth factors. For example, there is a bacterial hydrophilic polypeptide that self-assembles into a nanometer internal diameter pore to build a selective lipid body. Various enzymes can be utilized for the synthesis of peptides which contain amino acids that control three-dimensional protein structure and growth. Growth factors can be applied in gels or other carriers which regulate the rate of release of the growth factors and help maintain the growth factors and the carrier, at a desired location in the body. Time release capsules, granules, or other carriers containing growth factor can be activated by tissue pH, by enzymes, by ultrasound,

by electricity, by heat, by selected *in vivo* chemicals or by any other selected means to release the growth factor. The carrier can be resorbable or non-resorbable. Or, the growth factor itself can be activated by similar means. Either the carrier or the growth factor can mimic extracellular fluid to control cell growth, migration, and function. The growth factor can be administered orally, systemically, in a carrier, by hypodermic needle, through the respiratory tract, or by any other desired method. The growth factor an also be administered into a capsule or other man-made composition or structure placed in the body. While administration of the growth factor is presently usually localized in the patient's body, circumstances may arise where it is advantageous to distribute a growth factor throughout the patient's body in uniform or non-uniform concentrations. An advantage to growth factors is that they can often, especially when in capsule form or in some other containment system, be inserted to a desired site in the body by simply making a small incision and inserting the growth factor. The making of such small incision comprises minor surgery which an often be accomplished on an out-patient basis. The growth factors can be multifactorial and nonspecific.

PAGE 37, LINES 19-25

Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated. Likewise, any host cell, clone cell, cultured cell, or cell would work. Genetic switches (such as the insect hormone ecdysone) can be used to control genes inserted into humans and animals. These gene switches can also be used in cultured cells or other cells. Gene switches govern whether a gene is on or off making possible precise time of gene activity.

PAGE 44, LINE 19 – PAGE 46, LINE 16

Genetic material comprising a portion of a gene, a gene, genes, a gene product (i.e., a composition a gene causes to be produced like, for example, an organ-producing growth factor), growth factor, or an ECM (extracellular matrix) can be used in or on the body to grow an organ to tissue. For example, the vascular epithelial growth factor gene (VEGF) or its growth factor equivalent can be inserted into the body to cause an artery to grow. When insertion of a gene, portion of a gene, gene product, growth factor, or ECM *in vivo* or *ex vivo* is referred to herein in connection with any of the implant techniques of the invention, it is understood that a cell nutrient culture(s), physiological nutrient culture(s), carrier (s), enhancer(s), promoter(s), or any other desired auxiliary component(s) can be inserted with the gene or at the same location as the gene, growth factor, ECM, etc.

An artery is an organ from the circulatory system. An artery can be grown in the heart, legs, or other areas by injecting a gene or other genetic material into muscle at a desired site. Size, vascularity, simplicity of access, ease of exploitation, and any other desired factors can be utilized in selecting a desired site. The gene is one of several known VEGF genes which cause the production of vascular endothelial growth factors. Several VEGF genes which produce vascular endothelial growth factors are believed to exist because nature intends for there to be several pathways (i.e., genes) which enable the production of necessary growth factors. The existence of several pathways is believed important because if one of the genes is damaged or inoperative, other similar genes can still orchestrate the production of necessary growth factors. VEGF genes are used by the body to promote blood vessel growth. VEGF genes are assimilated (taken in) by muscle cells. The genes cause the muscle cells to make a VEGF protein which

promotes the growth of new arteries. VEGF proteins can be made in a lab and injected into a patient intravenously, intraluminally, or intramuscularly to promote the growth of an artery. Or, the genes (or other genetic material) can be applied with an angioplasty balloon, with the assistance of a vector, or by any other method.

It is not always desirable to grow a completely new organ. Sometimes growing a portion of an organ is desirable. For example, in some heart attacks or strokes, a portion of the heart or brain remains viable and a portion dies. An injection of a gene to form cardiac muscle and/or an injection of a gene to form an artery can be utilized to revive or replace the dead portion of the heart. The dead portion of the heart may (or may not) be used as a matrix while the new muscles and vessels grow. Thus, in this example, a partial new organ is grown in a pre-existing organ. A pacemaker may (or may not) be necessary. A second injection of a gene may (or may not) be necessary to stop cardiac muscle growth once it is completed. Portions of organs throughout the body can similarly be repaired or replaced. It may be necessary to provide gene(s) or growth factor(s) sequentially. For instance, one or more blood vessels are grown by inserting an appropriate gene or other genetic material into a selected area. Second, an appropriate gene or other genetic material is inserted in the selected area to grow a bone or other organ.

The size and shape limitation of the desired structure can come from a containment and boundary contact inhibition phenomenon or by a chemical inhibition.

A variation on the theme of growing a portion of an organ is as follows: a portion of a heart dies. The pericardium is utilized as a scaffold and seeded with cells and/or genes to grow new muscle, and genes (or other genetic material) to grow new arteries. Immediately adjacent the dead cardiac muscle, onto or into the pericardium, the appropriate cells, genes, and/or growth factors (or other genetic material) are placed. Once the new muscle and blood vessels have

grown, the function specific tissue can be applied to the damaged portion of the heart and paced, if necessary, to augment cardiac action. If the surgeon desires, the dead muscle can be removed and the new muscle and blood vessels can be surgically rotated into the excised region and secured. This probably can be done endoscopically. In essence, the pericardium is utilized to allow the new muscle wall to grow. The new muscle wall is then transplanted into the damaged heart wall. This procedure utilizes the body as a factor to grow an organ and/or tissue, after which the organ and/or tissue is transplanted to a desired region. On the other hand, the new muscle wall may integrate itself into the old wall and not require transplantation.

PAGE 47, LINE 22 – PAGE 48, LINE 15

Organs and/or tissues can be formed utilizing the patient's own cells. For example, a skin cell(s) is removed from the intraoral lining of a cheek. The cell is genetically screened to identify DNA damage or other structural and/or functional problems. Any existing prior art genetic screening technique can be utilized. Such methods can utilize lasers, DNA probes, PCR, or any other suitable device. If the cell is damaged, a healthy undamaged cell is, if possible, identified and selected. If a healthy cell can not [sic] be obtained, the damaged cell can be repaired by excision, alkylation, transition or any other desired method. A growth factor(s) is added to the cell to facilitate dedifferentiation and then redifferentiation and morphogenesis into an organ or function specific tissue. Any machine known in the art can be used to check the genetic fitness of the organ and its stage of morphogenesis. A cell nutrient culture may or may not be utilized depending on the desired functional outcome (i.e., growth of an artery, of pancreatic Islet cells, of a heart, etc.) or other circumstances. Replantation can occur at any appropriate stage of morphogenesis. The foregoing can be repeated without the patient's own

cells if universal donor cells such a [sic] germinal cells are utilized. Germinal cells do not require a dedifferentiation. They simply differentiate into desired tissues or organs when properly stimulated. Similarly, the DNA utilized in the foregoing procedure can come from the patient or from any desired source.

During reimplantation one of the patient's own cells is returned to the patient. During implantation, a cell not originally obtained from the patient is inserted on or in the patient.

In the example above, if germinal cells (and in some case, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.

EXHIBIT B

DISCLOSURES
APPLICATION SERIAL NO. 09/064,000

PAGE 33, LINES 8-10

Morphogenesis or morphogenetics is the origin and evolution of morphological characters and is the growth and differentiation of cells and tissues during development.

PAGE 40, LINE 20 – PAGE 43, LINE 3

EXAMPLE 11

MSX-1 and MSX-2 are the homeobox genes that control the generation and growth of a tooth. A sample of skin tissue is removed from the patient and the MSX-1 and MXS-2 homeobox gene(s) are removed from skin tissue cells. The genes are stored in an appropriate nutrient culture medium.

BMP-2 and BMP-4 growth factors are obtained by recombinant or natural extraction from bone.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

MXS-1 and MXS-2 transcription factors are obtained which will initiate the expression of the MXS-1 and MXS-2 homeobox genes.

The MXS-1 and MXS-2 transcription factors, BMP-2 and BMP-4 bone morphogenic proteins, and MXS-1 and MXS-2 genes are added to the nutrient culture medium along with the living stem cells.

EXAMPLE 12

Example 11 is repeated except that the transcription factors bind to a receptor complex in the stem cell nucleus.

EXAMPLE 13

Example 11 is repeated except that the MXS-1 and MXS-2 transcription factors are not utilized. The transcription of the MXS-1 and MXS-2 homeobox genes is activated by applying an electric spark to the nutrient culture medium.

EXAMPLE 14

Example 13 is repeated except that the stem cells are starved and the transcription of the MXS-1 and MXS-2 homeobox genes is activated by applying an electric spark to the nutrient culture medium.

EXAMPLE 15

WT-1 and PAX genes are obtained from a sample of skin tissue is removed from the patient. The genes are stored in an appropriate nutrient culture medium. PAX genes produce PAX-2 and other transcription factors.

BMP-7 and other kidney related BMP growth factors are obtained by recombinant or natural extraction from bone.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees.

The temperature of the culture medium can be varied as desired but ordinarily is between 40 and 102 degrees F.

The WT-1 and PAX genes, and BMP-7 and other kidney BMPS are added to the nutrient culture medium along with the living stem cells.

A primitive kidney germ is produced. The kidney germ is transplanted in the patient's body near a large artery. As the kidney grows, its blood supply will be derived from the artery.

EXAMPLE 16

The Aniridia gene is obtained from a sample of skin tissue is removed from the patient. The gene(s) is stored in an appropriate nutrient culture medium.

Aniridia transcription factor (activates expression of the Aniridia gene) and growth factors (function to help stem cells differentiate during morphogenesis to form an eye) are obtained.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

The Aniridia transcription factor and growth factors and the Aniridia gene are added to the nutrient culture medium along with the living stem cells.

A primitive eye germ is produced. The kidney germ is transplanted in the patient's body near the optic nerve. As the kidney grows, its blood supply will be derived from nearby arteries.

EXAMPLE 17

The Aniridia gene is obtained from a sample of skin tissue is removed from the patient. The gene(s) is stored in an appropriate nutrient culture medium.

Aniridia transcription factor (activates expression of the Aniridia gene) and growth factors (function to help stem cells differentiate during morphogenesis to form an eye) are obtained and added to the nutrient culture medium.

An eye germ develops. A branch of the nearby maxillary artery is translocated to a position adjacent the eye germ to promote the development of the eye germ. The eye germ matures into an eye which receives its blood supply from the maxillary artery.

The term "cell nutrient culture" as used herein can include any or any combination of the following: the extracellular matrix; conventional cell culture nutrients; and/or, a cell nutrient such as a vitamin. As such, the cell nutrient culture can be two-dimensional, three dimensional, or simply a nutrient, and is useful in promoting the processes of cellular dedifferentiation, redifferentiation, differentiation, growth, and development.

PAGE 44, LINES 12– 13

An organ, as used herein, consists of two or more kinds of tissues joined into one structure that has a certain task.

PAGE 48, LINES 13– 15

In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.

PAGE 53, LINE 1 – PAGE 56, LINE 25

EXAMPLE 18

A 36 year old Caucasian male experiences pain in his left leg. A medical examination reveals a damaged one inch long section of a large artery in his left leg. The examination also reveals that this damaged section of the artery is nearly completely clogged with plaque and that the wall of the artery is weakened. The weakening in the arterial wall makes attempting to clean out the artery risky and also makes it risky to attempt to insert a stent in the artery.

Recombinant cDNA encoded to combine with a cell ribosome to produce the human growth factor VEGF is assembled into a eukaryotic expression plasmid. The recombinant cDNA is from cDNA libraries prepared from HL60 leukemia cells and is known to cause the growth of arteries. The plasmid is maintained at a room temperature of 76 degrees F.

The clones are placed in 1.0 milliliters of a normal saline carrier solution at a room temperature of 76 degrees F to produce an genetic carrier solution. The genetic carrier solution contains about 250 ug of the cDNA clones. A nutrient culture can, if desired, be utilized in conjunction with or in place of the saline carrier. Each clone is identical. If desired, only a single clone can be inserted in the normal saline carrier solution. The saline carrier solution comprises 0.09% by weight sodium chloride in water. A saline carrier solution is selected because it will not harm the DNA clone.

Two sites are selected for injection of the genetic carrier solution. While the selection of sites can vary as desired, the sites are selected at the lower end (the end nearest the left foot of the patient) of the damaged section of the artery so that the new arterial section grown can, if necessary, be used to take the place of the damaged section of the artery in the event the damaged section is removed.

The first site is on the exterior wall of the artery on one side of the lower end of the damaged section of the artery. A containment system is placed at the first site.

The second site is inside the wall of the artery on the other side of the lower end of the artery.

The genetic carrier solution is heated to a temperature of 98.6 degrees F. 0.25 milliliters of the genetic carrier solution is injected into the containment system at the first site. 0.25 milliliters of the genetic carrier solution is injected at the second site inside the wall of the artery. Care is taken to slowly inject the genetic carrier solution to avoid entry of the solution into the artery such that blood stream will carry away the cDNA in the solution.

After two weeks, an MRI is taken which shows the patient's leg artery. The MRI reveals new growth at the first and second sites.

After four weeks, another MRI is taken which shows the patient's leg artery. The MRI shows that (1) at the first site a new artery is growing adjacent the patient's original leg artery, and (2) at the second site a new section of artery is growing integral with the original artery, i.e., at the second site the new section of artery is lengthening the original artery, much like inserting a new section of hose in a garden hose concentric with the longitudinal axis of the garden hose lengthens the garden hose.

After about eight to twelve weeks, another MRI is taken which shows that the new artery growing adjacent the patient's original artery has grown to a length of about one inch and has integrated itself at each of its ends with the original artery such that blood flows through the new section of artery. The MRI also shows that the new artery at the second site has grown to a length of one-half inch.

In any of the examples of the practice of the invention included herein, cell nutrient culture can be included with the gene, the growth factor, the extracellular matrix, or the environmental factors.

In any of the examples of the practice of the invention included herein, the concept of gene redundancy can be applied. For example, the Examples 1 to 14 concerning a tooth list the genes MSX-1 and MSX-2. These genes differ by only two base pairs. Either gene alone may be sufficient. A further example of redundancy occurs in growth factors. Looking at the Examples 10 to 14, BMP4 or BMP2 alone may be sufficient. Redundancy can also be utilized in connection with transcription factors, extracellular matrices, environmental factors, cell nutrient cultures, physiological nutrient cultures, vectors, promotors, etc.

One embodiment of the invention inserts genetic material (gene, growth factor, ECM, etc.) into the body to induce the formation of an organ. Similar inducing materials inserted ex vivo into or onto a living cell in an appropriate physiological nurturing environment will also induce the growth of an organ. The VCSEL laser allows early detection in a living cell of a morphogenic change indicating that organ formation has been initiated. With properly timed transplantation, organ growth completes itself.

During the ex vivo application of the invention, a gene and/or growth factor is inserted into a cell or a group of cells; an ECM or environmental factor(s) are placed around and in contact with a cell or group of cells; or, genetic material is inserted into a subunit of a cell to induce organ growth. An example of a subunit of a cell is an enucleated cell or a comparable artificially produced environment. In in vivo or ex vivo embodiments of the invention to induce the growth of an organ, the genes, growth factors, or other genetic material, as well as the environmental factors or cells utilized, can come from any desired source.

EXAMPLE 19

Genetically produced materials are inserted in the body to cause the body to grow, reproduce, and replace in vivo a clogged artery in the heart. This is an example of site-specific gene expression. A plasmid expression vector containing an enhancer/promoter is utilized to aid in the transfer of the gene into muscle cells. The enhancer is utilized to drive the specific expression of the transcriptional activator. After the enhancer drives the expression of the transcriptional activator, the transcriptional activator transactivates the muscle/artery genes. Saline is used as a carrier. Cardiac muscle can take up naked DNA injected intramuscularly. Injecting plasmid DNA into cardiac (or skeletal) muscle results in expression of the transgene in cardiac myocytes for several weeks or longer.

Readily available off-the-shelf (RAOTS) cDNA clones for recombinant human VEGF165, isolated from cDNA libraries prepared from HL60 leukemia cells, are assembled in a RAOTS expression plasmid utilizing 736 bp CMV promoter/enhancer to drive VEGF expression. Other RAOTS promoters can be utilized to drive VEGF expression for longer periods of time. Other RAOTS recombinant clones of angiogenic growth factors other than VEGF can be utilized, for example, fibroblast growth factor family, endothelial cell growth factor, etc. Downstream from the VEGF cDNA is an SV40 polyadenylation sequence. These fragments occur in the RAOTS pUC118 vector, which includes an Escherichia coli origin of replication and the Beta lactamase gene for ampicillin resistance.

The RAOTS construct is placed into a RAOTS 3 ml syringe with neutral pH physiologic saline at room temperature (or body temperature of about 37 degrees C). The syringe has a RAOTS 27 gauge needle.

Access to the cardiac muscle is gained by open heart surgery, endoscopic surgery, direction injection of the needle without incision, or by any other desired means. The cardiac muscle immediately adjacent a clogged artery is slowly injected with the RAOTS construct during a five second time period. Injection is slow to avoid leakage through the external covering of muscle cells. About 0.5 ml to 1.0 ml (milliliter) of fluid is injected containing approximately 500 ug phVEGF165 in saline (N=18). The readily available off-the-shelf cDNA clones cause vascular growth which automatically integrates itself with the cardiac muscle. Anatomic evidence of collateral artery formation is observed by the 30^{th} day following injection to the RAOTS construct. One end of the artery integrates itself in the heart wall to receive blood from the heart. The other end of the artery branches into increasing smaller blood vessels to distribute blood into the heart muscle. Once the growth of the new artery is completed, the new artery is left in place in the heart wall. Transplantation of the new artery is not required.

Blood flow through the new artery is calculated in a number of ways. For example, Doppler-derived flow can be determined by electromagnetic flowmeters (using for example, a Doppler Flowmeter sold by Parks Medical Electronic of Aloha, Oregon) both in vitro and in vivo. RAOTS external ultrasound gives a semiquantitative analysis of arterial flow. Also, RAOTS angiograms or any other readily available commercial devices can be utilized.

VEGF gene expression can be evaluated by readily available off-the-shelf polymerase chain reaction (PCR) techniques.

If controls are desired, the plasmid pGSVLacZ containing a nuclear targeted Beta-galactosidase sequence coupled to the simian virus 40 early promoter can be used. To evaluate efficiency, a promoter-matched reporter plasmid, pCMV Beta (available from Clontech of Palo

Alto, California), which encodes Beta-galactosidase under control of CMV promoter/enhancer can be utilized. Other RAOTS products can be utilized if desired.

EXAMPLE 20

A patient, a forty year old African-American female in good health, has been missing tooth number 24 for ten years. The space in her mouth in which her number 24 tooth originally resided is empty. All other teeth except tooth number 24 are present in the patient's mouth. The patient desires a new tooth in the empty "number 24" space in her mouth.

A full thickness mucoperiosteal flap surgery is utilized to expose the bone in the number 24 space. A slight tissue reflection into the number 23 tooth and number 25 tooth areas is carried out to insure adequate working conditions.

A Midwest Quietair handpiece (or other off-the-shelf handpiece) utilizing a #701XXL bur (Dentsply Midwest of Des Plaines, Illinois) (a #700, #557, #558, etc. bur can be utilized if desired) is used to excavate an implant opening or site in the bone. The implant opening is placed midway between the roots of the number 23 and number 25 teeth. The opening ends at a depth which is about fifteen millimeters and which approximates the depth of the apices of the roots of the number 23 and number 25 teeth. Care is taken not to perforate either the buccal or lingual wall of the bone. In addition, care is taken not to perforate or invade the periodontal ligament space of teeth numbers 23 and 25.

An interrupted drilling technique is utilized to avoid overheating the bone when the #701XXL bur is utilized to form the implant opening. During a drilling sequence, the drill is operated in five second increments and the handpiece is permitted to stall. Light pressure and a gentle downward stroke are utilized.

PAGE 62, LINES 1–10

EXAMPLE 36

Example 18 is repeated except that the patient is a 55 year old Caucasian male, and the genetic carrier solution is injected into two sites in the coronary artery of the patient. The first site is on the exterior wall on one side of the artery. The second site is inside the wall of the artery on the other side of the artery. A section of the artery is damaged, is partially blocked, and has a weakened wall. The first and second sites are each below the damaged section of the artery. Similar results are obtained, i.e., a new section of artery grows integral with the original artery, and a new section of artery grows adjacent the original artery. The new section of artery has integrated itself at either end with the original artery so that blood flows through the new section of artery.

EXHIBIT C

CLAIMS
APPLICATION SERIAL NO. 09/064,000

Claim 382 — A method for producing and integrating tissue consisting of a desired soft tissue at a selected site in a body of a human patient comprising:

(a) Placing cells in said body of said human patient;

(b) Forming a bud at said selected site in said body of said human patient; and

(c) Growing said desired soft tissue which integrates itself into said body of said human patient from said bud.

Claim 383 — The method of claim 382, wherein said cells are multifactorial and non-specific.

Claim 384 — The method of claim 383, wherein said cells comprise stem cells.

Claim 385 — The method of claim 382 further comprising forming a new artery.

Claim 386 — The method of claim 383 further comprising forming a new artery.

Claim 387 — The method of claim 382, wherein said soft tissue comprises mesodermal tissue.

Claim 388 The method of claim 382, wherein said soft tissue comprises an artery.

Claim 389 The method of claim 382, wherein said cells comprise stem cells.

Claim 390 The method of claim 389, wherein said soft tissue comprises an artery.

Claim 391 The method of claim 382, wherein said cells comprise pluripotent cells.

Claim 392 The method of claim 391, wherein said soft tissue comprises an artery.

Claim 393 The method of claim 391, wherein said cells comprise stem cells.

Claim 394 The method of claim 393, wherein said stem cells are multifactorial and non-specific.

Claim 395 The method of claim 382, wherein said cells are injected into said body.

Claim 396 The method of claim 382, wherein said cells are locally placed into said body.

Claim 397 The method of claim 396, wherein said cells comprise stem cells.

Claim 398 The method of claim 396, wherein said cells are injected intramuscularly.

Claim 399 The method of claim 397, wherein said stem cells are injected intramuscularly.

Claim 400 The method of claim 388 further comprising determining blood flow through said new artery.

Claim 401 The method of claim 388 further comprising observing said new artery.

Claim 402 The method of claim 399, wherein said selected site comprises a leg of said patient.

1: Trends Mol Med. 2001 Jun;7(6):259-64.

ELSEVIER FULL-TEXT ARTICLE

Related Articles, Links

Mesenchymal stem cells: building blocks for molecular medicine in the 21st century.

Caplan AI, Bruder SP.

Dept of Biology, Skeletal Research Center, Case Western Reserve University, Cleveland, OH, USA.

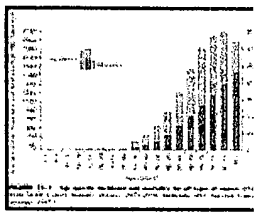
Mesenchymal stem sells (MSCs) are present in a variety of tissues during human development, and in adults they are prevalent in bone marrow. From that readily available source, MSCs can be isolated, expanded in culture, and stimulated to differentiate into bone, cartilage, muscle, marrow stroma, tendon, fat and a variety of other connective tissues. Because large numbers of MSCs can be generated in culture, tissue-engineered constructs principally composed of these cells could be re-introduced into the in vivo setting. This approach is now being explored to regenerate tissues that the body cannot naturally repair or regenerate when challenged. Moreover, MSCs can be transduced with retroviral and other vectors and are, thus, potential candidates to deliver somatic gene therapies for local or systemic pathologies. Untapped applications include both diagnostic and prognostic uses of MSCs and their descendents in healthcare management. Finally, by understanding the complex, multistep and multifactorial differentiation pathway from MSC to functional tissues, it might be possible to manipulate MSCs directly in vivo to cue the formation of elaborate, composite tissues in situ.

Publication Types:

- Review
- Review, Tutorial

PMID: 11378515 [PubMed - indexed for MEDLINE]

Cancer



Although cancer occurs in persons of every age, it is fundamentally a disease of aging. Sixty percent of new cancer cases and two thirds of cancer deaths occur in persons > 65 years (see Figure 72-1). The incidence of common cancers (eg, breast, colorectal, prostate, lung) increases with age. However, incidence of many cancers levels off after age 80, suggesting the possibility of intrinsic resistance to the development of cancer in late life or some selection bias.

The age-related increase in cancer incidence predicts that as the U.S. population ages, cancer incidence will continue to increase. There are several theoretical reasons why cance incidence increases in the elderly (see Table 72-1): age-related alterations in the immune system (decreased immune surveillance); accumulation of random genetic mutations leading to oncogene activation or amplification or decreased tumor-suppressor gene activity; lifetime carcinogen exposure (especially for colorectal and lung cancers); hormonal alterations or exposure; and long latency periods. There may be increased susceptibility to carcinogens, possibly caused by decreased DNA repair. Multiple genetic changes are necessary for the development of cancer, most clearly exemplified by the stepwise genetic changes shown by many colon polyps progressing to cancer. The exponential rise in many cancers with age fits with an increased susceptibility to the late stages of carcinogenesis by environmental exposures. Lifetime exposure to estrogen may lead to breast or uterine cancer; exposure to testosterone, to prostate cancer. The decline in cellular immunity may lead to certain types of cancer that are highly immunogenic (eg, lymphomas, melanoma).

Controversy continues over whether cancer is less aggressive in the elderly. Growth and metastasis of several types of cancer (breast, colon, lung, prostate) appear to be slower in the elderly. Yet, death occurs with smaller tumor burdens. Reasons for the difference in mortality appear to be complex: Diagnosis is often made later, treatment tends to be less aggressive, and competing causes of death are more likely; all of these factors result in shorter survival in older patients.

Risk Factors and Prevention

The part of cancer prevention we know the most about is the avoidance of toxins that induce or promote cancer. Induction refers to the earliest genetic change induced by a carcinogen. Promotion refers to cell growth induction that fixes and then further alters the genetic abnormality. Carcinogens may alter normal growth-promoting genes (proto-oncogenes), which are permanently turned on. They may also damage growth-suppression genes (tumor suppressors) such that they become permanently turned off. Both may be necessary to create a cancer. Since prolonged exposure is one of the necessary ingredients to both induction and promotion, prevention of cancer in the elderly must begin before people become old. The best evidence strongly recommends avoiding smoking, overuse of alcohol, and exposure to known toxic chemicals. Maintaining a low-fat, high-fiber diet may be helpful.

Hormonal exposure is implicated in the development of breast, prostate, and uterine cancers. Studies have been inconsistent as to whether exogenous estrogen exposure increases breast cancer risk, but the relative risk is probably in the range of 1.3. Early menarche, late menopause, and late or no pregnancies are confirmed risk factors. Estrogenic stimulation of the endometrium, when allowed to go unchecked, increases the risk of uterine cancer 2- to 2.5-fold.

Drugs may also reduce the risk of some cancers. Tamoxifen has recently been approved for breast cancer prevention. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) appear to reduce the risk of colon cancer. Retinoids may be helpful in reducing the risk of new primary squamous cell cancers in persons with previous such cancers related to tobacco use. The role of antioxidants in preventing cancers remains unclear. Inhibiting the conversion of testosterone to 5-α-dihydroxytestosterone may prevent prostate cancer.

Screening

Because cancer is more common in the elderly than in younger populations, screening is more likely to detect cancer in older populations. Cancers for which screening has proved beneficial in reducing mortality include breast, cervical, and colon cancer. It is unclear whether immune surveillance of early cancers is effective. Most cancers are poorly immunogenic and are unlikely to raise an immune response with low tumor volumes. With prostate-specific antigen (PSA) testing, prostate cancer is detected at an earlier stage, but most studies have not shown that screening with PSA reduces mortality. Screening for ovarian cancer, even in high-risk women, has proved disappointing.

Most published recommendations for cancer screening focus on populations younger than considered here. Thus, the main concern regarding the elderly is when to discontinue routine screening. No studies show benefit of screening past age 75 for any cancers. Despite the lack of data, recommendations on cancer screening in the elderly have been published (see Table 72-2).

Treatment

Research that focuses on cancer in younger populations may not be applicable to the elderly, the segment of the population at highest risk for cancer, leaving us with a paucity of knowledge on how best to manage cancer in the age group that experiences it most.

Treatment goals must be individualized based not only on treatability of the cancer, but also

on comorbid conditions, functional status (one of the best predictors of response and tolerance (see Table 81-3 and Table 81-4), social situation (which may preclude treatments involving travel or expense), and willingness of the patient to tolerate side effects of treatment. Surgery, chemotherapy, radiation therapy, and hormonal therapy are the mainstays of treatment. However, symptomatic and supportive therapy with analgesics, antidepressants, anxiolytics, and antiemetics, as well as support groups and individual and family counseling, must be integrated into treatment programs. Access to support services and to trained health care practitioners varies depending on the patient's geographic location, financial resources, mobility, and support of family and friends. Referral to major cancer centers may prolong survival but may not be the most humane course of action for debilitated and relatively immobile patients.

Age per se is not usually the deciding factor as to whether aggressive treatment is warranted: that decision must assess the likelihood that the cancer will respond to treatment, the extent of spread, comorbid conditions that could limit therapy, and the patient's wishes. Chemotherapy or radiation therapy should be strongly considered in clinical situations in which cure, prolonged survival, or definable palliation can be achieve with these modalities.

Chemotherapy: A variety of older chemotherapeutic drugs remain effective and useful. In addition, newer antineoplastics are becoming more commonly used in the treatment of cancer in the elderly (see Table 72-3). Chemotherapy may be less well tolerated by elderly patients because of kinetic and dynamic changes that occur with age, decreased organ reserve, and poorer wound healing. Comorbid conditions such as diabetic neuropathies, renal insufficiency, heart failure, and decubitus ulcers may contraindicate specific treatments. However, nausea and vomiting from chemotherapy tend to be less intense in th elderly.

Age-related decreases in liver size, blood flow, and metabolic reserve and use of drugs that inhibit cytochromes may inhibit drug metabolism. The neurotoxicity of drugs such as vincristine, cisplatin, and paclitaxel is especially troublesome in the elderly, and severe neuropathies or constipation may result. Hematopoietic toxicity of most drugs and of radiation therapy is increased to some degree. Gastrointestinal toxicities of 5-fluorouracil and doxorubicin may be increased, and frail patients are less able to tolerate short episodes of diarrhea or decreased oral intake from mucositis. Reduced cardiac reserve makes it more difficult for the elderly to tolerate anthracyclines, and decreased renal reserve decreases tolerance to platinum drugs and methotrexate, requiring adjustments in dose or choice of drug. With curable malignancies, great care must be taken not to reduce doses without documented need.

Advancements in hematologic manipulation have made the use of chemotherapy safer in the elderly. For example, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) diminish duration of chemotherapy-induced neutropenia. Erythropoietin is often effective in treating chemotherapy-induced anemia and is well tolerated. Oprelvekin, a nonspecific growth factor for megakaryocytes, has been approved for preventing and treating severe thrombocytopenia associated with chemotherapy. However, oprelvekin prevents, at most, 30% of needed platelet transfusions and often causes significant adverse effects (edema, dyspnea, tachycardia). It should be used with caution in patients at risk of heart failure or with central nervous system tumors. Pamidronate is effective treatment of tumor-induced hypercalcemia. Other bisphosphonate

may be as effective.

Antiserotonin antiemetics (ondansetron, granisetron, dolasetron) are more effective than older drugs and have few side effects. Dolasetron may cause a prolonged QT interval and therefore must be used with caution in patients at risk of ventricular arrhythmias. Expense is a major deterrent to the use of the antiserotonin antiemetics, and they lose effectiveness 48 to 72 hours after chemotherapy. Phenothiazines, benzodiazepines, and dexamethasone are more effective for delayed nausea.

Amifostine is a chemoprotectant that is beneficial in treating neurotoxicity and nephrotoxicity caused by cisplatin. Dexrazoxane is a cardioprotectant used with anthracyclines. The clinical usefulness of amifostine and dexrazoxane has not been fully defined.

Radiation therapy: This modality has become more tolerable and safer with newer technologies and improved techniques, such as high-energy linear accelerators, better control of target areas, three-dimensional CT planning, and improved dosimetry. Patients who have conditions such as arthritis, kyphoscoliosis, parkinsonism, or dementia may require special positioning or immobilization. The elderly appear to be at increased risk of radiation lung damage, coronary artery injury, esophagitis, and enteritis, necessitating precise planning and dosimetry. Mucositis, esophagitis, or enteritis may lead to more rapid dehydration in the elderly. Despite these problems, some seemingly frail elderly patients can tolerate radiation therapy.

Pain control: Pain control is especially important in the care of elderly cancer patients. Although pain control is often considered part of end-of-life care, persons with cancer may have chronic pain or intermittently painful complications of cancer during any stage of thei disease and it may continue over the course of many years. The goal is to achieve an acceptable level of pain control with tolerable adverse effects. Comfort must be emphasize and the patient reassured that pain will be aggressively managed. Treating the source of pain is important. Radiation therapy to painful bony or other lesions should be considered. Chemotherapy may be of palliative benefit.

Opioids are used to treat severe pain not relieved by NSAIDs. Addiction should not be an issue for prescribers, and patients should be reassured that fear of addiction should not affect their use of the drug. Timed-release morphine and oxycodone as well as transdermal fentanyl relieve baseline pain. Fast-acting drugs, such as hydrocodone, oxycodone, morphine, hydromorphone, and transmucosal fentanyl lollipops, relieve intermittent or breakthrough pain. Fentanyl clearance is decreased in the elderly. Methadone, meperidine, pentazocine, and propoxyphene should not be used in the elderly. Stimulant laxatives are essential for an elderly patient receiving opioid therapy.

Elderly patients may become somnolent while being treated with opioids. Methylphenidate taken periodically at a dose of 5 to 10 mg, is often useful, especially for those patients desiring more social interaction when taking opioids.

Pain not relieved by opioids requires adjunctive treatment. Antidepressants, anticonvulsants, or antiarrhythmics may be used for neuropathic pain. Epidural or intrathecal opioids or clonidine infusion may be extremely effective without causing side effects. Nerve blocks may be helpful for intra-abdominal or dermatomal distribution pain.

Pamidronate given intravenously monthly is effective at reducing bone pain in metastatic breast cancer, multiple myeloma, and probably prostate cancer. Radioactive strontium or samarium localizes in blastic bone metastases and reduces bone pain, but results have been less promising than first expected.

Nursing Issues

Oncology nursing is now a specialization of nursing. Oncology nurses educate and counsel patients and their families as well as administer chemotherapy, interpret and manage treatment-related side effects, coordinate community and medical services, and provide palliative care. Triage and initial management of problems in elderly cancer patients are often handled by nursing personnel with the use of standard protocols. The nurse must be able to recognize the altered presentations of illness and side effects in the elderly as well a pharmacologic differences in the use of commonly prescribed drugs. Examples of enhance side effects of drugs used in the elderly include increased risk of disorientation, light-headedness or falls from the use of antiemetics or opioids, and increased risk of dehydratio from drugs that cause vomiting and diarrhea in elderly patients with decreased thirst response. The oncology nurse is a key provider in assessing and managing pain because of the prolonged contact with patients in a variety of settings. The oncology nurse is also on the front lines of managing nutritional support and other symptoms.

Social Issues

Many social issues arise in the care of elderly cancer patients. These issues often become complex and require the expertise of a social worker or an interdisciplinary team. Services may have to be coordinated to help with home care, travel, meal preparation, and drug adherence. Counseling may be warranted to help patients and their families cope with the seriousness of the illness. Efforts to overcome these difficulties frequently require alterations in treatment plans and interdisciplinary approaches.

Finances may pose problems as well. Oral chemotherapy drugs are covered 80% by Medicare if there is also an approved IV form of the drug. Other drugs taken orally, including pain medications (especially timed-release formulations), can be very expensive and are not covered by Medicare. Most pharmaceutical companies have indigent patient programs.

End-of-Life Issues

It must not be forgotten that cancer is often fatal. Sometimes treatment becomes futile, exposing an elderly patient to suffering that outweighs any potential benefit. Even at the time of initial diagnosis, treatment is not always warranted. An honest discussion of what i likely to be gained and what the side effects of treatment are likely to be is the best course of action. Most patients understand when it is time to make a transition to more palliative goals of care (palliative care is defined by the World Health Organization as the active tota care of patients whose disease is not responsive to treatment). This understanding can be fostered by direct and forthright discussions regarding prognosis and benefits and risks of therapy and is enhanced by a trusting physician-patient relationship.

Involvement of hospice services early in the course of palliative care can be helpful. The financial benefits alone of switching to the Medicare hospice benefit may be substantial.

Hospice personnel have expertise in preparing patients and families spiritually, financially, and legally for the end of life.

Most patients wish to remain at home. Every effort should be made to accommodate this wish, but attention needs to be paid to caregiver burden. Short stays in a hospital or nursing home, which are covered by Medicare, may be necessary for respite to caregivers. Interventions and clinic visits should be kept to the minimum necessary for palliation. Although Medicare reimburses physicians for time spent on hospice issues, the reimbursement is rarely adequate and does not compensate for the amount of documentation required.

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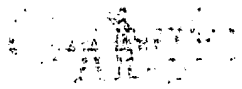

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Medical Dictionary

One entry found for **integrate**.

Main Entry: **in·te·grate**
Pronunciation: ˈint-ə-ˌgrāt
Function: *transitive verb*
Inflected Form(s): **-grat·ed**; **-grat·ing**
: to form or blend into a unified whole : cause to undergo integration <an *integrated* personality>
- **in·te·gra·tor** /-ˌgrāt-ər/ *noun*

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Merriam-Webster

Pronunciation Key

\ ə \ as **a** in abut	\ g \ as **g** in go	\ r \ as **r** in red
\ ˈə ɪə \ as **u** in abut	\ h \ as **h** in hat	\ s \ as **s** in less>
\ ᵊ \ as **e** in kitten	\ i \ as **i** in hit	\ sh \ as **sh** in shy
\ ər \ as **ur/er** in further	\ ī \ as **i** in ice	\ t \ as **t** in tie
\ a \ as **a** in ash	\ j \ as **j** in job	\ th \ as **th** in thin
\ ā \ as **a** in ace	\ k \ as **k** in kin	\ th̲ \ as **th** in the
\ ä \ as **o** in mop	\ k̲ \ as **ch** in ich dien	\ ü \ as **oo** in loot
\ aů \ as **ou** in out	\ l \ as **l** in lily	\ ů \ as **oo** in foot
\ b \ as in **b**aby	\ m \ as **m** in murmur	\ v \ as **v** in vivid
\ ch \ as **ch** in chin	\ n \ as **n** in own	\ w \ as **w** in away
\ d \ as **d** in did	\ ŋ \ as **ng** in sing	\ y \ as **y** in yet
\ e \ as **e** in bet	\ ō \ as **o** in go	\ yü \ as **you** in youth
\ ˈē ɪē \ as **ea** in easy	\ ȯ \ as **aw** in law	\ yů \ as **u** in curable
\ ē \ as **y** in easy	\ ȯi \ as **oy** in boy	\ z \ as **z** in zone
\ f \ as **f** in fifty	\ p \ as **p** in pepper	\ zh \ as **si** in vision

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TENTH EDITION

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integers under the operations of addition and multiplication form an *integral domain*〉

in·te·grand \'in-tə-ˌgrand\ *n* [L *integrandus*, gerundive of *integrare*] (1897) : a mathematical expression to be integrated

in·te·grate \'in-tə-ˌgrāt\ *vb* **-grat·ed; -grat·ing** [L *integratus*, pp. of *integrare*, fr. *integr-*, *integer*] *vt* (1638) 1 : to form, coordinate, or blend into a functioning or unified whole : UNITE 2 : to find the integral of (as a function or equation) 3 **a** : to unite with something else **b** : to incorporate into a larger unit 4 **a** : to end the segregation of and bring into equal membership in society or an organization **b** : DESEGREGATE 〈~ school districts〉 ~ *vi* : to become integrated

integrated *adj* (1922) 1 : marked by the unified control of all aspects of industrial production from raw materials through distribution of finished products 〈~ companies〉 〈~ production〉 2 : characterized by integration and esp. racial integration 〈an ~ society〉 〈~ schools〉

integrated circuit *n* (1962) : a tiny complex of electronic components and their connections that is produced in or on a small slice of material (as silicon) — **integrated circuitry** *n*

in·te·gra·tion \ˌin-tə-'grā-shən\ *n* (1620) 1 : the act or process or an instance of integrating: as **a** : incorporation as equals into society or an organization of individuals of different groups (as races) **b** : coordination of mental processes into a normal effective personality or with the individual's environment 2 **a** : the operation of finding a function whose differential is known **b** : the operation of solving a differential equation

in·te·gra·tion·ist \-sh(ə-)nist\ *n* (1951) : a person who believes in, advocates, or practices social integration — **integrationist** *adj*

in·te·gra·tive \'in-tə-ˌgrā-tiv\ *adj* (1862) : serving to integrate or favoring integration : directed toward integration

in·te·gra·tor \-ˌgrā-tər\ *n* (1876) : one that integrates; *esp* : a device or computer unit that totalizes variable quantities in a manner comparable to mathematical integration

in·teg·ri·ty \in-'te-grə-tē\ *n* [ME *integrite*, fr. MF & L; MF *integrité*, fr. L *integritat-*, *integritas*, fr. *integr-*, *integer* entire] (14c) 1 : firm adherence to a code of esp. moral or artistic values : INCORRUPTIBILITY 2 : an unimpaired condition : SOUNDNESS 3 : the quality or state of being complete or undivided : COMPLETENESS *syn* see HONESTY

in·teg·u·ment \in-'te-gyə-mənt\ *n* [L *integumentum*, fr. *integere* to cover, fr. *in-* + *tegere* to cover — more at THATCH] (ca. 1611) : something that covers or encloses; *esp* : an enveloping layer (as a skin, membrane, or husk) of an organism or one of its parts — **in·teg·u·men·ta·ry** \-'men-t(ə-)rē\ *adj*

in·tel·lect \'in-tᵊl-ˌekt\ *n* [ME, fr. MF or L; MF, fr. L *intellectus*, fr. *intellegere* to understand — more at INTELLIGENT] (14c) 1 **a** : the power of knowing as distinguished from the power to feel and to will : the capacity for knowledge **b** : the capacity for rational or intelligent thought esp. when highly developed 2 : a person with great intellectual powers

in·tel·lec·tion \ˌin-tᵊl-'ek-shən\ *n* (1579) 1 : an act of the intellect : THOUGHT 2 : exercise of the intellect : REASONING

in·tel·lec·tive \-'ek-tiv\ *adj* (15c) : having, relating to, or belonging to the intellect : RATIONAL — **in·tel·lec·tive·ly** *adv*

¹in·tel·lec·tu·al \ˌin-tᵊl-'ek-chə-wəl, -chəl, -shwəl\ *adj* (14c) 1 **a** : of or relating to the intellect or its use **b** : developed or chiefly guided by the intellect rather than by emotion or experience : RATIONAL **c** : requiring use of the intellect 2 **a** : given to study, reflection, and speculation **b** : engaged in activity requiring the creative use of the intellect — **in·tel·lec·tu·al·i·ty** \-ˌek-chə-'wa-lə-tē\ *n* — **in·tel·lec·tu·al·ly** \-'ek-chə-wə-lē, -chə-lē, -shwə-lē\ *adv* — **in·tel·lec·tu·al·ness** \-'ek-chə-wəl-nəs, -chəl-, -shwəl-\ *n*

²intellectual *n* (1615) 1 *pl, archaic* : intellectual powers 2 : an intellectual person

in·tel·lec·tu·al·ism \ˌin-tᵊl-'ek-chə-wə-ˌli-zəm, -chə-ˌli-, -shwə-ˌli-\ *n* (1838) : devotion to the exercise of intellect or to intellectual pursuits — **in·tel·lec·tu·al·ist** \-list\ *n or adj* — **in·tel·lec·tu·al·is·tic** \-ˌek-chə-wə-'lis-tik, -chə-'lis-, -shwə-'lis-\ *adj*

in·tel·lec·tu·al·ize \ˌin-tᵊl-'ek-chə-wə-ˌlīz, -chə-ˌlīz, -shwə-ˌlīz\ *vt* **-ized; -iz·ing** (ca. 1819) : to give rational form or content to — **in·tel·lec·tu·al·i·za·tion** \-ˌek-chə-wə-lə-'zā-shən, -chə-lə-, -shwə-lə-\ *n* — **in·tel·lec·tu·al·iz·er** \-'ek-chə-wə-ˌlī-zər, -chə-ˌlī-, -shwə-ˌlī-\ *n*

in·tel·li·gence \in-'te-lə-jən(t)s\ *n* [ME, fr. MF, fr. L *intelligentia*, fr. *intelligent-*, *intelligens* intelligent] (14c) 1 **a** (1) : the ability to learn

implies native ability or aptn
more substantial qualities 〈*cle*
ness in perceiving and unde
QUICK-WITTED implies promptr
devising expedients in momen
his *quick-witted* opponent〉.

in·tel·li·gent·sia \in-ˌte-lə-'jen(
fr. L *intelligentia* intelligence] (
tic, social, or political vanguard

in·tel·li·gi·ble \in-'te-lə-jə-bəl\
ligere] (14c) 1 : apprehensibl
being understood or compreh
'bi-lə-tē\ *n* — **in·tel·li·gi·ble·n
bly** \-blē\ *adv*

in·tem·per·ance \(ˌ)in-'tem-p(
esp : habitual or excessive drin

in·tem·per·ate \-p(ə-)rət\ *adj*
in- + *temperatus*, pp. of *tempe*
criticism〉; *esp* : given to exce
tem·per·ate·ly *adv* — **in·tem

in·tend \in-'tend\ *vb* [ME *ent*
pose, fr. L *intendere* to stretch
stretch — more at THIN] *vt* (1
: to proceed on (a course) 3
: to have in mind as a purpose
fied use or future ~ *vi*, *archai*

in·ten·dance \in-'ten-dən(t)s\
DENCE 2 : an administrative c

in·ten·dant \-dənt\ *n* [F, fr.
intendere to intend, attend]
governor) esp. under the Fren

¹intended *adj* (15c) 1 : expec
〈his ~ bride〉 2 : INTENTIONA

²intended *n* (1767) : the perso

intending *adj* (1788) : PROSPE

in·tend·ment \in-'ten(d)-mən
esp. of a law

in·ten·er·ate \in-'te-nə-ˌrāt\
tender — more at TENDER] (1
er·a·tion \-ˌte-nə-'rā-shən\ *n*

in·tense \in-'ten(t)s\ *adj* [ME
to stretch out] (15c) 1 **a** :
ment was ~〉 〈~ pain〉 **b** :
treme degree 〈~ colors〉 2
energy, determination, or co
strong feeling or earnestness
— **in·tense·ly** *adv* — **in·ten

in·ten·si·fi·er \in-'ten(t)-sə-ˌf
: INTENSIVE

in·ten·si·fy \in-'ten(t)-sə-ˌfī\
intense or more intensive : s
and contrast of (a photograp
make more acute : SHARPEN
sive : grow stronger or more
'kā-shən, -ˌten(t)-sə-\ *n*

in·ten·sion \in-'ten(t)-shən\
3 — **in·ten·sion·al** \-'tench
i·ty \-ˌten(t)-shə-'na-lə-tē\
-'ten(t)-shə-nᵊl-ē\ *adv*

in·ten·si·ty \in-'ten(t)-sə-tē\
of being intense; *esp* : extr
feeling 2 : the magnitude
(as of area, charge, mass, or

¹in·ten·sive \in-'ten(t)-siv\
intensity or intensification
: tending to strengthen or i
phasis 〈~ adverb〉 **c** : cor
to increase productivity by
rather than by increase in s
in·ten·sive·ness *n*

²intensive *n* (1813) : an inte

intensive care *n* (1963) :
taking care of seriously ill p